

## **REMARKS**

By this Amendment, Claims 1, 5, 12, 22, 23 and 34 are amended. Claims 11 and 47 are canceled. Claims 1, 3-10, 12-19, 21-35, 45, 46, 48 and 49 are pending in this Application. Support for the amendments can be found in the Specification, e.g., page 32, last two paragraphs and claims as filed, e.g., amended and canceled claims. "Substituted by" has been amended to "replaced by" in accordance with the Examiner's suggestion. It is clear from the atoms specified that these are replacements and not substituents. The text of claim 5 above differs from text in the specification in that commas are removed from the expression "lymphoid tissue type follicular reticulum cell sarcoma". The commas were possibly interpreted as setting out three elements of the group rather than the one intended. Applicants attach a reference (Andriko et al.) supportive of the singular nature of the element. No issue of new matter arises. Applicants respectfully request reconsideration and withdrawal of the rejections set forth in the March 30, 2006 Office Action, readdressed in the August 10, 2006 Advisory Action and respectfully request allowance of all pending claims.

### **Substance of Interview**

Applicants gratefully acknowledge the courtesies extended to their representative by Examiner Berch in a September 8, 2006 interview at the United States Patent and Trademark Offices. Substance of the interview is summarized here and incorporated in the following remarks.

Examiner Berch clarified his reasoning underlying rejections in the pending Office Action. While Applicants do not agree that the requests for documentation should be deemed proper, to advance prosecution, Applicants provide relevant documents in their possession. For example, Applicants were specific in reciting "CDK". Thus, an interpretation expanding the clear meaning of this term would properly be dismissed with no more than a clarifying statement in the record. However, for a clearer record, a reference demonstrating recognition in the art of a distinction between certain CDK-like molecules and CDK is attached.

The Examiner explained that regarding R4 and R5, the "or" was interpreted as providing a distinct definition, not related to the R4 and R5 defined previously in the claim. The Examiner clarified that he believed that although generally accepted in the art, the monocyclic vs. heterocyclic nature of the ring should be explicit. Appropriate amendment is made even more clearly reciting the R4/R5 component

Rejections under 35 U.S.C. §112, second paragraph

Claims 1, 3-19, 21-35 and 45-49 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The Office Action includes several numbered paragraphs setting forth these rejections. Applicants respectfully traverse these rejections in corresponding numbered paragraphs.

1. The Office Action alleges that the scope of claim 22 is unclear.

Claim 22 is amended to recite specific CDKs. Applicants reserve the right to claims reciting the genus in later prosecution of this or a continuation/divisional application. Applicants believe that the issue of indefiniteness is thereby obviated. Reconsideration and withdrawal of this rejection are respectfully requested.

2. Claim 23 was alleged to be unclear. The Office Action indicates that the wording of the claim does not provide for inhibition of a complex, only the CDK component of the complex. Applicants respectfully traverse this rejection, but nevertheless amend the claim to recite inhibition of the complex. The complex is a multi-component complex that contains a CDK as the active component of the complex. The claim rightfully features inhibition of the activity component, that is the CDK and now also the complex. The complex *per se* has kinase activity stemming from activity of the CDK. Thus whether one characterizes the CDK or the complex as being inhibited, the same activity is inhibited. Thus no issue of new matter arises in the amended claim. In view of this explanation reconsideration and withdrawal of this rejection are respectfully requested.

3. The Office Action stands by an assertion that cyclin D does not exist. In fact multiple cyclin Ds are recognized, e.g., D1, D2 and D3, as mentioned in the Office Action. The art clearly recognizes proper uses of the term "cyclin D". For example medterms.com provides the following description:

**Cyclin D:** A family of three closely related proteins termed cyclin D1, D2 and D3 that are expressed in an overlapping redundant fashion in all proliferating cell types and collectively control the progression of cells through the cell cycle. Since the D-cyclins are essential to cell division, they may also be involved in cancer.

Google indicates over a quarter million hits for "cyclin D". Clearly there is such entity as understood in the art. However, as offered in the February 16, 2006 Reply, claim 23 is amended to incorporate subject matter of claim 47, now canceled. Applicants believe that this amendment obviates the rejection. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

4. As discussed above, claims are amended as suggested by the Examiner to obviate this rejection. Reconsideration and withdrawal of this rejection are respectfully requested.

5. The Office Action has maintained a rejection relating to =O substituents. The basis for maintaining the rejection rests on a theory that in order to bind an O to a ring C, two Hs must be replaced. This is not true. Each carbon in, for example, a benzene structure has four bonds, two required to maintain the ring structure, a delocalized or resonant bond and a bond to a H (or a substituent on a substituted ring). Thus each carbon of for example a benzene ring may bond an =O and remain in the ring structure simply by translocating from the atom a H (or substituent) bond and replacing the delocalized or resonant bond with a bond to the oxygen. The previous reply explained how this species was found in equilibrium with hydroxyl substituted conjugated molecules or aromatics. Applicants stand by the observations in the art that such structures exist. Although no declaration is believed necessary, Applicants offer to provide one if the Examiner remains unconvinced. Since the =O is inherently present in certain equilibrium circumstances, other language in the claim is deemed to cover this event. The oxo containing molecule would form tautomers featured in the claims. Accordingly, to advance prosecution and simplify issues should an appeal be necessary, Applicants have amended claim 1 above, without changing the scope, but not explicitly reciting "=O". Applicants respectfully submit that this aspect of the rejection is now obviated. Reconsideration and withdrawal of this rejection are respectfully requested.

6. The term "alkylene" was objected to as used with saturated and unsaturated. Applicants have provided an amended claim set where the appropriate definition from the specification is inserted into the claims to replace the language objected to. Reconsideration and withdrawal of this rejection are respectfully requested.

7. The term "heterocyclic" is objected to. The problem as stated in the Office Action is that "the rest of the ring is undefined". Applicants learned from the Examiner that his broadest reasonable interpretation meant that the "or" began a new definition of R4 and R5. The antecedent basis of the text preceding the "or" is made explicit by amendment and the nitrogen is defined as the heteroatom. Reconsideration and withdrawal of this rejection are respectfully requested.

8. Claim 47 was rejected as not further limiting claim 23. As offered in the February 16, 2006 Reply claim 47 is canceled, its language having been inserted into claim 23. This rejection is thereby believed to be obviated. Reconsideration and withdrawal of this rejection are respectfully requested.

9-11. Mixed type of neoplasm was alleged to be unclear, but was interpreted by the Office Action not to mean “a mixed neoplasm in the ordinary sense”. Claim 11 is cancelled. Claim 5 is amended to qualify what is meant by “mixed type of neoplasm”. Reconsideration and withdrawal of this rejection are respectfully requested.

12. The Office Action maintained the rejection relating to “phenyl”. Applicants respectfully assert that paragraph 21 of the previous reply sufficiently addressed which phenyl was referenced. The phenyl referred to was the phenyl referenced above in the claim. As amended the claim is even more clear in this regard. The office action also objected to the reference to both unsubstituted and substituted phenyls in conjunction with “where phenyl is substituted” language. Applicants respectfully submit that the skilled artisan would have understood the language in reference to phenyl substituents to apply only when they were present. But to render moot the Examiner’s objection, claim 1 is amended above to clarify antecedent basis and to insert the phrase “when substituted” to indicate that the list of substituents does not apply when no substituents are present. Reconsideration and withdrawal of this rejection are respectfully requested.

**Rejection under 35 U.S.C. §112, first paragraph: written description**

Claim 12 was rejected under 35 U.S.C. §112, first paragraph as allegedly going beyond teachings of the original specification. Claim 12 is amended above to obviate this rejection. Support for the amendment can be found in the specification as filed, for example in the original claims 3 and 12. Reconsideration and withdrawal of this rejection are respectfully requested.

**Rejection under 35 U.S.C. §112, first paragraph: enablement**

Claims 3-22, 24-26 45, 46 and 49 were rejected under 35 U.S.C. §112, first paragraph as allegedly requiring undue experimentation to practice the claimed invention. Applicants gratefully acknowledge the Examiner’s indication that claims 1, 21, 23, 27-35, 47 and 48 are not subject to this rejection. Claim 20 was previously canceled and claim 11 is canceled herewith. Thus with respect to claims 11 and 20 reconsideration and withdrawal of the rejection is deemed proper. With respect to claims 3-10, 12-19, 21-22, 24-26, 45-46 and 49 Applicants respectfully traverse this rejection. The numbers below correspond to the numbers set forth in the March 30, 2006 Office Action.

*General Background*

The *Wands* opinion was cited in the Office Action as is used herein as a guide to compare the various factors with those of the present invention. *Wands* concluded:

**Considering all of the factors, we conclude that it would not require undue experimentation to obtain antibodies needed to practice the claimed invention.**

*Wands* required millions if not billions of cells. Thus, outcomes were unpredictable because millions if not billions or more of antibodies were possible. Only very few working examples (4) were shown out of the many millions or billions possible. The majority sampled were non-working examples.

The Office Action at page 30 expressed a problem understanding Applicants response. See, e.g., page 30, penultimate paragraph. "Applicants (sic) response here is not entirely understood. . . ." Applicants provide the following explanation of relevance.

Non-working or inoperative embodiments are discussed in the case law and deemed acceptable in the literal claim scope. Case law defining the scope of enablement allows some amount of inoperative embodiments, even when inoperative embodiments outnumber operative embodiments are tolerated and do not render a claim invalid. This topic is discussed below in reference to specific issues raised in rejection.

**(1)(a) Scope of compounds.** The Office Action indicates that the scope of the claims that includes the Ra variable and several X substituents covers a multitude of compounds. This is identified as a factor to be considered according to *Wands*. The Office Action while citing this number provides no basis what the relationship to undue experimentation might be. Numbers alone, even high numbers such as those encountered in *Wands*, by themselves are not indicative of undue experimentation. Applicants respectfully submit that the specification provides more than adequate guidance and teaching with respect to the various Ra variables. See e.g., the tabular data beginning at page 67. The Office Action has not cited any basis that the number of possible embodiments would lead undue experimentation to practice the instantly claimed invention with any one or even several of the embodiments selected. Indeed, the specification, for example at pages 117-168, provides a multitude of data describing attributes and effects of various embodiments of Ra. Depending on the chosen Z, claim 1 recites different acceptable Ra embodiments.

The -Z-Ra portion of the molecule is not the portion responsible for binding the CDK. This variable portion modifies the basicity (charge in aqueous environment) of the N to which Z is attached and as embodied in the claims serves to minimize uptake of the compound by red blood cells. Minimizing uptake of the compounds by the red blood cells is significant because red blood cells make up almost half the volume of blood. When the compound is sequestered within a red blood cell the compound cannot freely pass from the plasma to target tissues.

Similar molecules without the improvement provided by the  $-Z-Ra$  were not sufficiently active *in vivo* because rapid uptake by the red blood cells made the compound unavailable for the intended targets. With this guidance, undue experimentation cannot be properly deemed as implicated. The examples teach the skilled artisan a wide range of substituents whose tendency is to improve the bioavailability. The CDK reactive portion is maintained in all examples. Thus at least this factor does not favor a *Wands* based rejection.

(b) Scope of Diseases Covered. From pages 7 to 20, the Office Action mentions and describes a large plurality of diseases, yet does not set forth any reason why administration of a compound of claim 1 would require undue experimentation. Regardless of the disease, administration can be accomplished without undue experimentation. All the recited diseases involve hyperproliferation involving the cell cycle. See, e.g., Sherr and Roberts (attached). Inhibition of CDKs affects cell cycle for CDK discussion in relation to cell cycle. Thus each of the recited diseases is proper in the claims. Thus this factor fails to support a *Wands* based rejection.

With respect to apoptosis, Applicants respectfully submit that there is no requirement in the claim language that the blocking or augmenting of apoptosis has to be in all cells as could be inferred from the Office Action. The Examiner has noted multiple (at least three) paths to apoptosis. Applicants respectfully submit the Examiner's comments relating to too little apoptosis may find mitigation in slowing proliferation of cells rather than proliferating and then inducing apoptosis.

**(2) The nature of the invention and predictability in the art.** Complexity of the animal system is cited, including a listing of growth factors. Three apoptotic mechanisms are mentioned. Besides a listing of normal and pathologic physiologic functions and discussion of several, there is no indication that practicing the instant claims would require undue experimentation. Though these comments are made there is no explanation of any relationship to undue experimentation, the test of whether an invention is enabled. The burden is on the Office to establish a *prima facie* support for any rejection. This burden is not met. Thus analysis focused on this factor fails to support a *Wands* based rejection.

**(3) Direction or Guidance.** The Office Action acknowledges a teaching of dosing from 0.02-1mg/kg/day. This range was criticized as being totally generic for the range of disorders. The Office Action notes that some anti-cancer drugs have foundered. Yet *Wands* exemplifies that inoperative embodiments, even if they outnumber operative embodiments, do not rise to undue experimentation. Furthermore the citation of experimentation on drugs that foundered is

evidence that such experimentation is in fact routine, not undue. The Office Action fails to make a case that experimentation required to practice the claimed invention would be considered undue. This factor fails to support a *Wands* based rejection.

(4) **State of the Prior Art.** The Examiner states that he is unaware of art that might render piperidinyl-amino purines obvious or anticipated when used as anticancer agents as featured in the instant claims. The Advisory Action explains this as indicative that the close art does not teach, suggest or enable use of the compounds of the present invention in this context.

Applicants respectfully submit that merely because similar compounds may not have successfully achieved any arbitrary task cannot be taken as indicative that undue experimentation would be required in the present context. With respect to the diseases recited, all recited disease involve hyperproliferation. The compounds of the present invention have been shown to act against proliferation. Thus they would be expected to ameliorate or treat these diseases. Applicants attach a review article as evidence of the involvement of CDKs in many diverse diseases. See, e.g., Knockaert et al. Figs. 1 and 3. Thus the broad applicability of CDK inhibitors is accepted in the art. This factor is yet another that fails to support a *Wands* based rejection.

(5) **Working Examples.** The Office Action alleges a lack of working examples in treating any specific disease. The Office Action further alleges that despite evidence of modulating CDK activity as shown in TABLE 2, the noted effects cannot be generalized to other CDKs. Applicants respectfully note that the claim amendments now recite specific CDKs (1, 2 and 4). While not commenting in detail on the extent of generalizing one might accurately make, Applicants respectfully submit that for any CDKs (if they might be found to exist) unaffected by one or more of the instant compounds, only routine, not undue experimentation would be required to identify inoperative embodiments. *Wands* is instructive that when even a majority of embodiments are inoperative, the experimentation is presumed to be undue. *Atlas Powder* 750 F.2d 1569, 1576-77 (CAFC 1984), a pre-*Wands* case) supports this reasoning:

We agree with the district court's conclusion on enablement. **Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid.** "It is not a function of the claims to specifically exclude ... possible inoperative substances..." *In re Dinh-Nguyen*, 492 F.2d 856, 858-59, 181 USPQ 46, 48 (CCPA 1974) (emphasis omitted). Accord, *In re Geerdes*, 491 F.2d 1260, 1265, 189 USPQ 789, 793 (CCPA 1974); *In re Anderson*, 471 F.2d 1237, 1242, 176 USPQ 331, 334-35 (CCPA 1973). Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid. See, e.g., *In re Cook*, 439 F.2d 730, 735, 58 CCPA 1049, 169 USPQ 298, 302 (1971). That, however, has not been shown to be the case here. [Bolding added.]

Similarly, there is no showing in this case that one of ordinary skill in the art would be required to experiment unduly to identify possible CDKs that might be refractory and thus represent inoperative embodiments. Once again, analysis of this factor mitigates against a *Wands* based rejection.

**(6) Skill of those in the art.** The Office Action submits that cancer therapy remains unpredictable. As a corollary the Advisory Action submits that more experimentation is involved. Such experimentation is routine in such important fields as cancer therapy. The Office Action has made no showing that any experimentation that might be required to practice the present invention would be considered undue. Specifically with respect to cancer therapies, Applicants respectfully recall teachings in the specification, for example in Table 3. A cross section of cancers, both solid and liquid is included. Applicants respectfully submit that these data support broad applications of the compounds of the invention, especially as relate to cancers. Analysis of this *Wands* factor does not support a 35 U.S.C. §112 enablement rejection.

Similarly, the Office Action covers several pages describing nuanced differences in autoimmune disease. Differing mechanisms are cited. Yet unifying features such as cellular proliferation are ignored. While some autoimmune diseases require cytokinesis, others may not. But they all require proliferation of cells to effect the disease state. A tool or compound that takes advantage of the similarities for effect need not specifically affect each difference that might be cited when a common element in disease progression is noted. The Office Action ignores the issue that for an enablement rejection to be deemed proper, a *prima facie* case that undue experimentation and not just routine experimentation would be required must be established. The Office Action fails in this regard.

As discussed above, in introducing this rejection, undue experimentation is the test used to determine enablement. The Office Action fails to appreciate the case law surrounding enablement, in this particular instance, the issue of non-working or inoperative embodiments. Applicants trust that the discussion above adequately addresses this issue.

Later in the same paragraph, the Office Action makes note that the specification fails to teach what is known in the art, for example, with respect to B-cells (a cell type mentioned in the previous November 17, 2005 Office Action). The Advisory Action comments that Applicants: "have not shown that their compounds do, in fact, prevent the activation, etc. of B-cells. In fact, the examiner cannot even locate, in this 183 page specification, even any mention of applicants compounds having any effect (sic) at all on B-cells." (T and B cells were discussed by the Examiner e.g., at page 19 of the November 17, 2005 Office Action. Applicants' comments with

respect to B Cells was intended as a response to the issue brought up in this context by the Examiner.) Whether explicit in the application or merely known in the art, the fact remains that in B-cell (antibody mediated) autoimmune disease, B-cell proliferation is a component. Thus inhibiting hyperproliferation of, in this instance, B-cells would have the expected effect of at least ameliorating symptoms of autoimmune disease. Thus, this discussion is pertinent to the 35 U.S.C. §112, first paragraph, enablement rejection.

The remainder of the section relating the 35 U.S.C. §112, first paragraph, enablement rejection similarly avoids the issue of the level and quality of experimentation, for example, whether routine or undue experimentation might be implicated. Differences in various embodiments, without more, do not support a conclusion that undue experimentation would be required.

In summary, while the Office Action has covered many pages with discussions of diseases and successful and failed treatments, nowhere is the quantity and quality of experimentation shown to be undue. In the absence of such *prima facie* showing, this rejection cannot be deemed proper. Reconsideration and withdrawal of this rejection are respectfully requested.

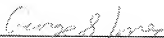
#### **Double Patenting**

Applicants gratefully acknowledge the Examiner's indication of a double patenting issue. However, since no claims have yet been deemed allowable, the final form and number of the claims that might issue in this application is unknown. A terminal disclaimer at this time is premature as any claim(s) that might issue may or may not be deemed obvious over claims 1-10 of USP 6,861,524.

Conclusion

In view of the above amendments and remarks, Applicants respectfully submit that the application is now in condition for allowance and request prompt indication of such. Should the Examiner wish to suggest additional amendments that might place the application in even better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below. Applicants are prepared to file a Terminal Disclaimer to effect immediate issuance of a Notice of Allowance if the Examiner indicates allowability of claims to which such Disclaimer would apply.

Respectfully submitted,

  
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